Kidney International, Vol. 38 (1990), pp. 668–672

Organization of collecting duct intercalated cells

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In recent years, the phenomenology of collecting duct HCO_3 transport has been well described. It is clear that the cortical collecting duct (CCD) of both the rat and rabbit secretes HCO_3 if the animal has been alkali-loaded, whereas this nephron segment absorbs HCO_3 if the animal has been acid-loaded [1–13]. The outer medullary collecting duct (OMCD) reabsorbs, but does not secrete, HCO_3 [4, 7, 14–19]. In contrast to HCO_3 transport in the CCD, HCO_3 reabsorption in the OMCD is unaffected by acid-base status [4, 7, 15].

Transport by two basic types of cells, the α (or A-type) and the β (or B-type) intercalated cells (ICs), appears to account for collecting duct HCO_3 absorption and secretion, respectively. Models of these cells are shown in Figure 1. The evidence as shown in the figure for H^+ATPases, Cl-HCO_3 exchangers, and basolateral Cl channels was recently presented in depth [20]. Both types of ICs have a high density of mitochondria [21] and contain abundant carbonic anhydrase [22–25]. Both have an electrically high-resistance apical membrane [26–29]. Both IC types contain H^+ATPase by immunocytochemical staining [30–32]. Taken in the conglomerate, the available evidence strongly supports the composite α and β cell models as shown. Thus the α cell, abundant in the OMCD, absorbs HCO_3 via H^+ secretion, whereas the β cell secretes HCO_3 via apical Cl-HCO_3 exchange [20].

This review considers in more detail three selected aspects of intercalated cell function that currently appear to represent areas of uncertainty: 1) possible species differences in intercalated cell organization between the rat and rabbit, 2) the possible role of an H^+-K^+ATPase in collecting duct HCO_3 reabsorption, and 3) the possible role of an apical Cl channel in β intercalated cells. Future data in these areas will probably force revision of the basic α and β cell models shown in Figure 1.

Possible species differences in β intercalated cells

The models shown in Figure 1 represent a composite drawn from data in the rat, rabbit, and human collecting ducts, and from the analogous mitochondria-rich cells of the turtle bladder. It is worthwhile, however, to highlight some of the inter-species differences that have emerged to date, particularly between the rat and rabbit.

The evidence for an apical Cl-HCO_3 exchanger in the β IC is strongest for the rabbit CCD. Schwartz, Barasch and Al-Awqati showed that intracellular pH (pH_i) falls in β ICs upon imposing a lumen-to-bath Cl gradient, a change consistent with accelerated extrusion of cell HCO_3 across the apical membrane via a Cl-HCO_3 exchanger [33]. Weiner and Hamm have recently investigated this exchanger further [34]. They found that lowering lumen [HCO_3] from 25 to 5 mM at a constant lumen [Cl] (125 mM) also caused a fall in pH_i. However, the same lowering of lumen [HCO_3] in the absence of lumen Cl caused no change in pH_i. Under voltage-clamp conditions (high [K] plus valinomycin), removal of lumen Cl reversibly alkalinized β cell pH_i, a result consistent with an apical electroneutral Cl-dependent HCO_3 extrusion pathway.

The evidence for a similar apical β cell Cl-HCO_3 exchanger in the rat, however, is only inferential. As alluded to above, the isolated, perfused rat CCD dissected from $NaHCO_3$-loaded or alkalotic animals does secrete HCO_3 [7, 11, 12]. Moreover, net HCO_3 secretion in the rat CCD perfused in vitro [11, 12], as well as in the in vitro perfused rat late distal tubule [8], requires luminal Cl. However, the process of HCO_3 secretion in the rat has not been studied at the single-membrane level using measurements of pH_i as it has been studied in the rabbit. There are no markers for β ICs in the rat equivalent to peanut lectin binding in the rabbit, and therefore there are no obvious candidates for a probe that might be useful in attempts to isolate the rat apical exchanger.

Beyond the mere lack of data concerning the β cell exchanger in the rat, there is evidence that the actual distribution of vacuolar H^+ATPase may, in fact, differ in the rat versus the rabbit. Stone and co-workers [35, 36] and Gluck and co-workers [37–40] have purified bovine kidney medullary H^+ATPase, and have sequenced and raised antibodies to various subunits of the enzyme. Extensive immunocytochemical studies in the rat by Brown and co-workers using Gluck's antibodies have shown that some CCD ICs have H^+ATPase labelling at the apical membrane, some at the basolateral membrane, and some in a diffuse pattern [30, 31, 41]. Coupled with the observation that ICs with apical H^+ATPase have, by immunocytochemistry, a basolateral Cl-HCO_3 exchanger [42], these data in the rat strongly argue for the α and β cell models shown in Figure 1. One possible qualification, however, is raised by an ultrastructural observation in the rat. Although Verlander, Madsen and Tischer were able to readily differentiate α from β ICs by scanning and thin-section transmission electron microscopy, and although α ICs had "studs" (the transmission electron microscopic equivalent of H^+ATPase) at the apical plasma membrane as expected, these investigators found no evidence for "studs" either at the apical or basolateral membrane of β ICs [43]. This negative result stands in distinction to similar

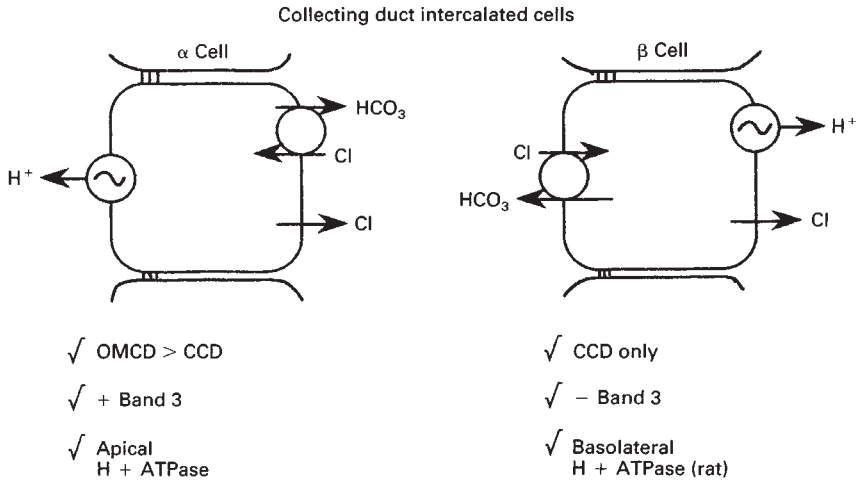

Fig. 1. *Model of transport proteins in collecting duct α and β cells.* Details are in the text.

studies in the turtle bladder, in which definite studs at the basolateral membrane were observed in the β cell [44]. Nonetheless, on the whole the evidence for a polarized distribution of H^+ATPase in rat ICs is convincing.

On the other hand, in the rabbit CCD studies by Ridderstrale et al and by Schuster and Gluck suggest that H^+ pumps in that species may not be so well polarized as in the rat, at least in β ICs [25, 32]. In the former study, rod-shaped intramembranous particles (the freeze-fracture equivalent of H^+ATPase) were found in both the apical and the basolateral membranes of all ICs. In unpaired comparisons, Ridderstrale et al found that the density of rod-shaped particles was significantly higher in apical versus basolateral membranes (1400 ± 150 vs. 649 ± 150/μm^2). In three cells, the particles could be counted in both membranes, and were also found to be more abundant in the apical (1600 ± 200/μm^2) than in the basolateral (290 ± 100/μm^2) membrane. No ICs were found in which the density of rod-shaped particles in the basolateral membrane exceeded that of the apical membrane [25]. In complementary studies, Schuster et al immunocytochemically labeled rabbit CCDs with Gluck's antibodies to the bovine medullary H^+ATPase [32]. As had been described in the rat CCD [42], these investigators found apical labelling of rabbit α cells (defined as ICs with basolateral Cl-HCO_3 staining). On the other hand, no ICs were found with preferential basolateral H^+ATPase staining; rather, putative β ICs had diffuse staining across the cell [32].

Taken together, these results in the rabbit suggest that the basolateral H^+ extrusion mechanism may involve a H^+ pump different from the apical α-type H^+ATPase. Perhaps the basolateral H^+ATPase in the rabbit β cell is an immunologically distinct isoform of the α-type apical pump. Testing this hypothesis will require epitope-specific monoclonal antibodies to the rabbit kidney H^+ATPase.

H^+-K^+ATPase in OMCD HCO_3 reabsorption

Recent evidence has raised the possibility that at least part of the HCO_3 reabsorption by the OMCD is not due to an H^+ATPase of the vacuolar family [45]. Rather, a substantial amount of HCO_3 reabsorption (H^+ secretion) may be due to a H^+-K^+ATPase (of the "E_1-E_2 type") similar to that found in the gastric mucosa [46–51].

Enzymatic activity corresponding to H^+-K^+ATPase activity has been demonstrated in both rat and rabbit CCD [47, 48]. Wingo and Straub recently examined the functional equivalent of this enzymatic activity [46, 51]. They reported that luminal addition of omeprazole, which inhibits the gastric H^+-K^+ATPase, abolished HCO_3 reabsorption and K^+ absorption by the rabbit OMCD without producing a change in transepithelial voltage [46]. Subsequent studies also showed inhibition of OMCD K^+ absorption by a more specific inhibitor of H^+-K^+ATPase, that is, by the compound SCH28080 [51]. The observation that HCO_3 absorption was completely abolished by omeprazole without a change in voltage suggests that most, if not all, HCO_3 absorption by the OMCD is mediated by an electroneutral H^+-K^+ATPase rather than by an electrogenic vacuolar H^+ATPase. It is not clear at present how to integrate these results with previous data. Immunocytochemical localization of vacuolar H^+ATPase in normal rabbits shows it to be localized at the apical membrane of rabbit OMCD ICs [32], whereas immunocytochemical localization of H^+-K^+ATPase in normal rabbits shows it to be diffusely distributed across the cell [49]. Also, the inhibition of basolateral HCO_3 exit in rabbit OMCD by disulfonic stilbenes or basolateral Cl removal is accompanied by a fall in the lumen-positive voltage, results which are consistent with acidification by an electrogenic (that is, vacuolar) H^+ pump [52].

There are several possible caveats in inhibitor and antibody studies that attempt to identify either vacuolar or H^+-K^+ATPases. First, it is possible that even the "specific" H^+-K^+ATPase inhibitor SCH28080 is not specific for that enzyme. In this regard, Graber and Devine recently reported that apical SCH28080 completely abolished H^+ secretion by the turtle bladder [53]. These data are consistent with a lack of specificity of SCH28080. Of course, they are also consistent with the previously unrecognized presence of H^+-K^+ATPase in the turtle bladder, and this will require further study. As discussed above for the vacuolar H^+ATPase, epitope-specific monoclonal antibodies can give insights into subtle structural differences between enzyme isoforms. In this regard, only a subset of antibodies to the gastric enzyme labels the kidney (G. Sachs, personal communication), suggesting that the kidney enzyme shares epitopes with the gastric pump, but is not

identical to it. Nonetheless, the kidney enzyme is probably very closely related to the gastric enzyme: high-stringency Northern blot analysis by Okusa et al, using a gastric H^+-K^+ATPase cDNA probe, detected a single band in rat kidney that co-migrated with the gastric mRNA band. Cross-hybridization of the H^+-K^+ATPase cDNA probe to the homologous Na^+-K^+ ATPase mRNA was excluded [50]. Finally, at least in the rat, K depletion causes the translocation of immunoreactive H^+-K^+ATPase from a diffuse pattern to the apical membrane of OMCD ICs [49]. Taken together, these observations suggest that there may be an important role for a renal H^+-K^+ATPase in mediating collecting duct HCO_3 reabsorption.

Apical Cl channel in β intercalated cells

Light and co-workers have recently reported finding an apical Cl conductance by patch-clamp methods in freshly isolated, peanut-lectin-positive rabbit CCD cells in primary culture [54]. This channel had a large conductance (303 pS), was activated upon excision from the cell (suggesting that it had been tonically inhibited in the cell-attached configuration), and was inhibited by several Cl channel blockers including the stilbene DIDS and the blocker diphenylamine carboxylate. Cl channel activity did not appear to be activated by changes in cytosolic $[Ca^{++}]$ within the physiological range, by dibutyryl cAMP, or by changes in pH_i. Of particular interest, the Cl-to-HCO_3 permeability ratio of the channel was only 1.5 to 1, suggesting that the channel could mediate electrogenic HCO_3 secretion under appropriate circumstances.

Several aspects of these results should be considered in context. First, previous microelectrode studies had demonstrated that the apical membrane of rabbit β-type ICs had a very low total ionic conductance and was devoid of any appreciable Cl conductance [26]. Although these previous results at first appear to be inconsistent with those of Light et al, it should be noted that the Cl channel identified by patch-clamp was generally only appreciated once the patch was excised from the cell, and thus would not be appreciated by microelectrode measurements on intact cells [54].

Second, the finding of an apical β cell Cl channel may explain certain previous observations. Schuster reported that the addition of 8-bromo-cAMP plus HCO_3 to isolated, perfused rabbit CCDs increased the transepithelial conductance and the flow of "equivalent current" (negative charge lumen-to-bath). This current appeared to be carried by (or at least required the presence of) Cl. The increase in equivalent current was well-matched by an increase in lumen-to-bath ^{36}Cl flux, and the increment in lumen-to-bath ^{36}Cl flux could not be accounted for by stimulation of 1:1 Cl-HCO_3 exchange [55]. These observations are consistent with a stimulation of a Cl conductive pathway by the combination of 8-bromo-cAMP and HCO_3. (Of note, HCO_3 also appears to be important in opening basolateral Cl channels in the rabbit CCD in the presence of cAMP [56]). Although Light et al failed to find activation of the β cell apical Cl channel by dibutyryl-cAMP, their experiments were done in the absence of HCO_3, so it is not clear whether the stimulus provided was adequate for channel opening.

In this regard, similar data in the turtle bladder should be recalled. Rich, Dixon and Clausen recently reported that 8-bromo-cAMP plus the phosphodiesterase inhibitor IBMX, in HCO_3-containing solutions, caused an increase in apical membrane area as measured by capacitance. This new apical membrane was Cl-selective [57]. These experiments reinforce the observations made earlier by Stetson et al [44] and by Sataki et al [58] in the turtle bladder, in which evidence was presented in favor of electrogenic HCO_3 secretion. Stetson et al [44] postulated that this HCO_3 secretion occurred via the operation of a moderately stilbene-sensitive apical Cl-HCO_3 exchanger in parallel with an apical Cl-selective (or HCO_3-selective) channel. In this way, Cl brought into the β cell via Cl-HCO_3 exchange could be recycled back out into the apical solution via the Cl channel [44].

In further considering the apical membrane of rabbit β ICs, it should be noted that VanAdelsberg et al have reported HCO_3 secretion by β cells in primary culture that is stilbene-sensitive [59], whereas HCO_3 secretion by the isolated CCD is relatively stilbene-insensitive [5]. Taken with the data on the Cl channel described by Light et al [54] (that is, degree of inhibitor sensitivity and the Cl:HCO_3 selectivity ratio near unity), it appears that the organization of rabbit CCD β cell apical membrane transporters, at least in cells in primary culture, and the function of β cell apical membrane transporters in the turtle bladder may turn out to be quite similar.

Summary

Our understanding of the mechanisms by which the collecting duct transports HCO_3 continues to evolve rapidly. The models put forth in Figure 1, though esthetically pleasing by virtue of their simplicity, will undoubtedly require modification as the above areas and others continue to be explored.

It should be noted that a large percentage of the citations in this review emanate from colleagues of Dr. Donald Seldin who have been or currently are nephrologists at Southwestern Medical School in Dallas [4–6, 10, 16–18, 20, 32, 34–36, 46, 49, 51, 52, 55]. The length of this list is testimony to the large number of investigators in the field of renal acid-base research who have been intellectually stimulated by their contact with Dr. Seldin.

Acknowledgments

Work in the author's lab is supported by NIH grant DK 38095 and by an Established Investigatorship of the American Heart Association.

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